FIBRINOLYTIC ACTIVITY IN RHEUMATOID ARTHRITIS

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INTRODUCTION

In rheumatoid arthritis, the build up of fibrin within the joint may be responsible for some form of chronic inflammation and joint manifestations including pannus formation and polymorph induced cartilage destruction (Belch et al., 1984).

An elevated plasma fibrinogen is a well recognised feature of active rheumatoid arthritis (RA), and the presence of large amount of fibrin in the synovial fluid and membrane is also well documented in this disease (Back Anderson & Gormsen, 1976).

Defective fibrinolytic activity has been demonstrated in many inflammatory conditions such as: rheumatoid arthritis (Belch et al., 1984), systemic lupus erythematosus (SLE) (Chu et al., 1988) and Behcet's syndrome (Gunliffe, 1973). However, the exact

clinical implication of defective fibrinolytic activity in various rheumatic conditions is still as yet a controversy.

Therefore, we have decided to study the fibrinolytic activity of the peripheral blood in patients with RA in relation to some clinical and laboratory manifestations in those patients.

MATERIAL AND METHODS

The present study included 15 patients with definite or classical rheumatoid arthritis, diagnosed according to the American Rheumatism Association criteria (Ropes et al. 1959). They were 10 females and 5 males. Their disease duration ranged from 12 months to 20 years (median 3 years). Patients were selected from the outpatient clinic of the Department of Physical Medicine & Rehabilitation

at Mansoura University Hospital.

All patients were receiving various

antirheumatic therapy including non-

steroidal antiinflammatory drugs

(NSAIDs) and corticosteroids in the

form of prednisolone and prednisone.

The dose ranged from 2.5 to 10 mg/

day. Patients continued their treat-

ment during the study period. Patients

with severe cardiac, hepatic or renal

disease were excluded, obese, diabet-

ics and smokers were also excluded.

A group of 10 apparently healthy sub-

jects were also included in the study

as a control group.

All patients were subjected to :

1- Full clinical examination of

the locomotor system with

particular attention to assess-

ment of :

* Joint pain (4 point scale, Jaffe,

1974).

* Duration of morning stiffness

(in minutes).

* Grip strength, measured with

a modified sphygmomanome-

ter cuff inflated up to 30

mmHg.

* Articular index (Ritchie et al ,

1968).

Plain antero-posterior and lateral
radiographs of both hand and wrist
and other affected joints.

III. Radiological examination :

3. Determination of euglobulin
clot lysis time (ECLT)
(Chakrabarti et al., 1968).

2. Fibrinogen-fibrin degrada-
tion products (FDPs)
(Chakrabarti et al., 1968).

1. Fibrinogen determination
(Clauss, 1957).

* Fibrinolytic activity in the blood
was assessed using :

* IgM rheumatoid factor (latex
test), erythrocyte sedimenta-
tion rate (ESR)(mm/h) wester-
gross total white cell count
(WBC), haemoglobin concen-
tration (Hb) (mg/dL) and
platelet count.

The following were measured ac-
cording to standard laboratory meth-
ods:

II. Laboratory investigations :

* Functional grading accord-
ing to Steinbrocker et
al.(1949).

Assessment of disease activity

In RA patients:

The degree of disease activity in RA patients was assessed using both clinical and laboratory criteria combined in a composite active index (CAI). This index is expressing the overall disease activity as one single score. The details of the calculation of this index are described elsewhere (Youssef et al., 1987).

In this work we used only two laboratory criteria (ESR & Hb). According to this index patients were divided into 2 groups :

Group one : consisted of 10 RA patients with active disease. Their composite index score ranged from 19 to 33 (median 25).

Group two : Comprised 5 RA patients with inactive disease. Their composite index score ranged from 7 to 13 (median 11).

RESULTS

The results of the present study are demonstrated in tables (1, 2, 3 & 4).

DISCUSSION

Defective fibrinolytic activity in patients with RA has been claimed by many authors (Van de Putte, 1977 and Belch et al., 1984). However, disease activity and details of drug therapy in those patients were not fully investigated.

In the present study, however, the relationship between fibrinolytic activity and disease activity was revealed. Therefore, fibrinolytic activity in our RA patients was found to be enhanced. This was manifested by short ECLT and an increase in the level of FDPs. ECLT measures mainly the activity of plasminogen activators in absence of fibrinolytic inhibitors (Van Kaula & Schultz, 1958 and Owen, 1969). The significant increase in plasma fibrinogen can be explained by the fact that fibrinogen is an acute phase protein (Takeda, 1969).

This was confirmed by its positive correlation with most of the clinical and laboratory criteria used in the assessment of disease activity. Furthermore, it correlates with a composite activity index based on the combination of both criteria (Youssef et al., 1987). Therefore, fibrinogen alone can not be used in the assessment of fibrinolytic activity as compared to con-

trols, and serial measurements should

be performed.

Our finding that fibrinolytic activity

in RA patients is enhanced rather than impaired is surprising. However, our

results show an interesting significant

correlation between ECLT, FDPs and

disease activity as measured by the

CAI. This correlation shows clearly

that fibrinolysis is increased with the

increase in disease activity. Therefore,

disease activity is an important varia-

ble affecting fibrinolysis and must be

considered.

The significantly negative correla-

tion of plasma fibrinogen with the

functional status of RA patients, may

be due to the fact that fibrin deposition

produces chronic inflammatory arthri-

tis via its action as an autoimmunogen

or by the production of chemotactic

derivatives which perpetuate the in-

flammation by neutrophils (Belch et

al., 1984). Organization of fibrin de-

posits will ultimately lead to fibrosis of

the synovial membrane, this may in-

terfere with cartilage nutrition, which

depends on a functioning synovial

membrane (Bach Anderson & Gorm-

sen, 1976). This ultimately may affect

the patients functional ability.

Fibrin is not normally found in joints

presumably because of continuous fib-

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formation.

Furthermore, we have also shown

that variations in disease activity can

be added as factors which affect the

rate of fibrinolysis. In addition, it was

shown that antirheumatic drugs can

also enhance fibrinolysis (Fearnley et

al., 1966 and Cunliffe et al., 1975).

These variations might be ex-

plained by the presence of inhibitors in

fibrin clot resulting in delayed fibrin

dissolution and enhancement of its

observed by many investigators

(Belch et al., 1986).

RA joints might be due to inadequate

joint fibrinolysis (Berger et al., 1977

and Van de Putte et al. 1977). Howev-

er, variation in the magnitude of fibrin-

olysis in some patients with RA was

that unusual build-up of fibrin found in

1983). Therefore, it has been claimed

factors of fibrinolysis present (Beck,

five proportion of activators and inhibi-

tor protein plasminogen. The rate of

by the cleavage of its inactive precur-

1972). This is produced when required

ated by plasmin (Astrup & Thorsen,

enzymatic degradation, which is medi-

brin, once it is formed is related to its

(Jasani, 1978). Normally the fate of fi-

production of plasminogen activators

rinolysis within the joint by increased

These drugs were shown to increase fibrinolytic activity by raising the level of circulating plasminogen activators and consequently reduce clot-lysis time (Chakrabarti et al., 1968 and Belch et al., 1986).

Moreover, antirheumatic drugs increase tissue fibrinolytic activity and that the inflamed tissues are their target of action in RA (Cunliffe et al., 1975). Therefore, the increased fibrinolytic activity observed in our patients with RA as expressed by shortened ECLT and increase FDPs, can be explained partly by the fact that most of them were treated with NSAID and corticosteroids. However, we found that the effect of antirheumatic drugs in our patients was less marked and overwhelmed by increase in disease activity, since most of our patients had an active disease (10 out of 15) and all of them were receiving almost the same anti-rheumatic drugs.

SUMMARY

This study was carried out to investigate whether there is a defective fibrinolytic activity or not in patients with rheumatoid arthritis (RA). 15 patients with RA, and 10 apparently healthy controls were included. In RA, various clinical and laboratory criteria were used to assess disease activity. Fibrinolytic activity in the blood was as-

sessed using: plasma fibrinogen, fibrinogen/fibrin degradation products (FDPs) and euglobin clot lysis time (ECLT). Patients with RA were found to have an enhanced fibrinolytic activity manifested by a significant shortening of ECLT ($P < 0.01$) and a significant increase in FDPs concentration ($P < 0.01$). Disease activity as measured by a composite activity index (CAI) showed an inverse correlation ($r_s = 0.74$, $P < 0.001$) with ECLT and a positive correlation with FDPs ($r_s = 0.71$, $P < 0.001$) and fibrinogen ($r_s = 0.77$, $P < 0.001$). In RA patients a significant correlation was found between plasma fibrinogen and morning stiffness ($r_s = 0.88$, $P < 0.001$), grip strength ($r_s = 0.63$, $P < 0.02$), articular index ($r_s = 0.78$, $P < 0.001$) and functional status ($r_s = 0.78$, $P < 0.001$), ESR ($r_s = 0.87$, $P < 0.001$) rheumatoid factor ($r_s = 0.6$, $P < 0.02$) and number of platelets ($r_s = 0.76$, $P < 0.001$). The increased fibrinolytic activity observed in RA patients may be due to an increase in disease activity.

Therefore, enhanced fibrinolytic activity in RA might be considered as one of the body defence mechanisms.

In conclusion : We have demonstrated enhanced fibrinolytic activity with increased disease activity in RA. Therefore, disease activity should be considered during the assessment of fibrinolytic activity in RA patients.

Table (1) (A&B) : Clinical (A) and laboratory (B) criteria in patients with rheumatoid arthritis (group 1).

(A)

Sex	Age	Duration	Pain	M. S.	G. S (mmHg)	F. C.	M. I.
M	F	(years)	(score)	(minutes)	Rt	Lt	(grade)
5	20						(score)
Range	22-70	1-20	1-3	2	60	80	90
Median		3	2	15-120	60-130	60-150	1-3
							2
							14

M. S. = Morning stiffness
 F. C. = functional classification
 G. S. = Grip strength
 A. I. = Articular index

(b)

Hb	gm/dL	E. S. R.	(mm.h)	R. F.	(titre)	Fibrinogen	(mg/dL)	E. C. L. T.	(minutes)	F. D. Ps.	µg/ml
Range	8-14	10-115	0-160	210-510	416	30-160	0-80	Median			

Hb = Haemoglobin
 ECLT = euglobin clot lysis time
 RF = Rheumatoid factor
 ESR = Erythrocyte sedimentation rate
 FDPs = fibrinogen / fibrin degradation products

Table (2) : Fibrinogen, ECLT and FDP's in patients with rheumatoid arthritis (R.A) compared to controls.

	Control group No. = 10	R. A. group No. = 25
* Fibrinogen (mg/dL)		
Range	235-340	210-510
Median	261	415
U		20
P		<0.002
* ECLT (minutes)		
Range	100-200	30-160
Median	180	90
U		36
P		<0.02
* F. D. Ps (µg/ml)		
Range	0-10	0-80
Median	5	30
U	-	-
P		<0.002

ECLT = Euglobin clot lysis time.

FDPs = Fibrinogen / fibrin degradation products.

U = Mann-Whitney test.

P = Probability test.

Table (3) (A&B) : Shows correlation between fibrinogen level (mg/dL) and some clinical criteria (A) and laboratory criteria (B) (Group I).

(A)		(B)	
M. S	Pain	G. S	A. I.
(minutes)	(Score)	(mmHg)	(grade)
Fibrinogen (mg/dL)	rs 0.88	-0.63	0.78
No. = 15	p <0.001	N. S.	<0.001

(b)

(b)		(A)	
E. S. R.	Hb	R. F.	Platelets
(mm/h)	(g/dL)		(mm)
Fibrinogen (mg/dL)	rs 0.87	-0.32	0.76
No. = 15	p <0.001	N. S.	<0.001

MS = Morning stiffness.
 AI = Articular index.
 Hb = Haemoglobin.
 rs = Spearman's rank correlation coefficient.
 p = Probability test.
 N. S = Not Significant.
 G. S = Grip Strength.
 F. C = Functional Classification.
 R. F = Rheumatoid Factor.

Table (4) : Correlation between enhancement of fibrinolytic activity as assessed by euglobin clot lysis time and fibrinogen / fibrin degradation products (FDPs) and disease activity of RA assessed by composite activity index.

Composite activity index (CAI)		P	
rs			
* Euglobin clot lysis ECLT	- 0.74	< 0.001	
* FDPs	0.71	< 0.001	
* Fibrinogen	0.77	< 0.001	

rs = Spearman rank correlation coefficient.
 p = Probability test.

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الملخص العربى

نشاط مذيبيات تحليل الفيبرين فى مرضى الروماتويد المفصلى

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يهدف هذا البحث إلى دراسة ما إذا كان هناك نقص أو زيادة فى نشاط مذيبيات تحليل الفيبرين فى مرضى الروماتويد المفصلى وكذلك إلى دراسة العلاقة بين نشاط مذيبيات تحليل الفيبرين والأعراض الاكلينيكية والدلالات المعملية المستخدم لقياس نشاط هذا المرض. وقد أشتمل هذا البحث على ١٥ مريضاً بمرض الروماتويد المفصلى وعلى عشرة أشخاص أصحاء للمقارنة. ولقد أستخدمت دلالات اكلينيكية ومعملية مختلفة بالإضافة إلى قياس معامل نشاط المرض الشامل الذى يشمل مزج قياس الدلالات الاكلينيكية والمعملية معاً. وقد تم قياس نشاط تحليل الفيبرين باستخدام قياس الفيبرينوجين - زيادة تكسير الفيبرينوجين - قياس زمن تحليل الايوجلوبين - وقد أظهر مرض الروماتويد المفصلى زيادة مذيبيات تحليل الفيبرين وقد أستدل عليه بنقص زمن تحليل الايوجلوبين وزيادة نواتج تكسير الفيبرينوجين فى عينات مرضى الروماتويد عنه فى عينات المجموعة الضابطة بالدم. وقد أظهر البحث وجود علاقة عكسية بين نقص زمن تحليل الايوجلوبين ومعامل نشاط المرض الشامل وكذلك وجود علاقة موجبة بين زيادة نواتج تكسير الفيبرينوجين وهذا المعامل. بالإضافة إلى ذلك ارتبطت زيادة نسبة الفيبرينوجين فى البلازما بزيادة واضحة فى بعض الأعراض الاكلينيكية والمعملية المستخدمة فى قياس نشاط المرض. ومن ذلك يمكن استنتاج أن زيادة نشاط تحليل مذيبيات الفيبرين فى مرضى الروماتويد المفصلى قد ترجع أساساً إلى الزيادة الواضحة فى نشاط المرض لهؤلاء المرضى ومن ذلك يمكن اعتبارها كخطوة ذاتية للدفاع عن الجسم.